Complex Regional Pain Syndrome: A Review of Diagnostics, Pathophysiologic Mechanisms, and Treatment Implications for Certified Registered Nurse Anesthetists

Daniel Watts, RN, BS
Michael J. Kremer, CRNA, PhD, FAAN

The pathophysiologic mechanisms for complex regional pain syndrome (CRPS) are complex and elusive. The proposed etiologic mechanisms for CRPS include inflammatory responses, peripheral or central sensitization, and sympathetic dysfunction. Anesthesia care of patients with CRPS is challenging. Treatments including physiotherapy, peripheral vasodilators, sympathetic blockade, analgesics, and other systemic medications can help optimize mobility, perfusion, and pain relief for affected patients.

Keywords: Chronic regional pain syndrome, history, taxonomy, treatment.

Objectives
At the completion of this course, the reader should be able to:
1. Discuss the symptoms of complex regional pain syndrome.
2. Delineate the diagnostic criteria for complex regional pain syndrome.
3. Review the major pathophysiologic mechanisms of complex regional pain syndrome.
4. Describe the role of sympathetic dysfunction in complex regional pain syndrome.
5. Discuss interventional and pharmacologic therapies for chronic regional pain syndrome.

Introduction
The diagnosis of complex regional pain syndrome (CRPS) is based on the history of the patient, symptoms, and findings at the time of diagnosis. A diagnosis of CRPS requires the existence of regional pain and sensory changes after a noxious event. The pain is associated with symptoms that may include abnormal skin color, temperature change, abnormal sudomotor activity (sweat gland stimulation), and/or edema. The severity of these findings in combination results in continuing pain that is disproportionate to any inciting event. There are 2 recognized types of CRPS: type 1 occurs without detectable nerve trauma. Minor injuries or a limb fracture may precede the onset of symptoms. Type 2 CRPS develops following injury of a major peripheral nerve. Often, research and scientific literature do not differentiate between CRPS 1 and CRPS 2. The terms CRPS 1 and CRPS 2 will be used when referencing material that discriminates between these 2 types of CRPS. Incorporation of biological, psychological, and social concepts, resulting in a comprehensive biopsychosocial model, has also been suggested to explain the genesis and maintenance of chronic pain.

Diagnosis and Clinical Manifestations
A diagnosis of CRPS is based on clinical criteria, and, to
date, there is no “gold standard” for its diagnosis or any objective diagnostic tool.\textsuperscript{3-9} The official CRPS taxonomy was proposed during a 1994 consensus workshop attended by clinicians and scientists with backgrounds in pain medicine and neurology. These workshop participants developed a standardized set of criteria that were broad, inclusive, and appropriate for clinical and research purposes. The International Association for the Study of Pain (IASP) later adopted the criteria and taxonomy, which include the following:\textsuperscript{10,11}:

- The presence of an initiating noxious event or a cause of immobilization
- Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event
- Evidence at some time of edema, changes in blood flow in the skin, or abnormal sudomotor activity in the region of pain
- No condition present that would otherwise account for the degree of pain and dysfunction
- CRPS 1 and 2 entail the described signs and symptoms of CRPS. CRPS 1 does not involve major nerve damage, while CRPS 2 includes nerve damage.

Systematic validation research findings found that these criteria had high sensitivity, but reports of specificity range from 0.36 to 0.60, leading to the potential for overdiagnosis of CRPS.\textsuperscript{3-7} A consensus group endorsed criteria for research (sensitivity, 0.70; specificity, 0.95) and clinical use (sensitivity, 0.70; specificity, 0.69) that improved the specificity from the IASP criteria.\textsuperscript{5,10} The following proposed diagnostic criteria for CRPS await endorsement by the IASP:\textsuperscript{5,10}:

- Continuing pain disproportionate to any inciting event
  - At least 3 of the 4 symptom categories:
    1. Sensory: hyperesthesia
    2. Vasomotor: temperature asymmetry and/or skin color changes and/or skin color asymmetry
    3. Sudomotor/edema: edema and/or sweating changes and/or sweating asymmetry
    4. Motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
  - At least 2 positive sign categories:
    1. Sensory: hyperalgesia (to pinprick) and/or al-lodynia (to light touch)
    2. Vasomotor: temperature asymmetry and/or skin color changes and/or asymmetry
    3. Sudomotor/edema: edema and/or sweating changes and/or sweating asymmetry
    4. Motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia, neglect) and/or trophic changes of the hair, nails, or skin. Trophic changes can include wasting away of the skin, tissue or muscle; thinning of the bones; and changes in the growth or hair or nails, including thickening or thinning of hair or brittle nails.

Diagnostic tests used to rule out CRPS have ranged from plain radiographs to electromyography, nerve velocity conduction studies, 3-phase bone scintigraphy, and magnetic resonance imaging scans and Doppler flow measurement. These tests all have low specificity for CRPS. More recently, neurophysiologic techniques such as transcranial magnetic stimulation, magnetoencephalography, and functional magnetic resonance imaging studies have been used to elucidate pathologic central signal processing changes that may be consistent with CRPS. Other psychophysical analytic techniques have been used to assess and quantify behavioral disturbances, vascular dysfunction, and neurobehavioral changes.\textsuperscript{11,12}

Genetic factors, including mutations in voltage-gated sodium channels, may be involved in CRPS, based on the occurrence of familial cases and several genetic association studies.\textsuperscript{13,14} Genetic assays can determine CRPS prevalence and susceptibility, as demonstrated in a study of the human leukocyte antigen (HLA) system in which 2 HLA alleles were found to be significantly associated with CRPS.\textsuperscript{14}

Although diagnostic criteria for CRPS exist, the clinical manifestations of this syndrome are variable. Most often, CRPS occurs after physical trauma or surgery and predominantly affects women. At least 50,000 new cases of CRPS 1 occur annually in the United States within the general population.\textsuperscript{15} A study in the Netherlands documented that 44% of patients with CRPS had a precipitating fracture and found the upper extremities to be more commonly affected.\textsuperscript{16} There is a paucity of epidemiologic data on CRPS.\textsuperscript{17} Its incidence has been estimated to include 1% to 2% of all fractures, 2% to 4% of all fractures with peripheral nerve injuries, and as many as 35% of Colles fractures.\textsuperscript{18} A retrospective review of 140 patients with CRPS at the Mayo Clinic, Rochester, Minnesota, found that 16% of cases occurred after surgery, with the majority being orthopedic.\textsuperscript{19} Complex regional pain syndrome is poorly understood, and there is scant information on the typical course of the disease. Although changes in the diagnostic criteria have clarified identification of this syndrome, generalizable epidemiologic data regarding CRPS are not available.\textsuperscript{17}

Complex regional pain syndrome evolves through different stages. The duration of each stage may be variable.\textsuperscript{20-23} Clinicians and researchers have described cases categorized into 3 major sequential stages. The first stage describes the acute changes related to pain and sensory disturbances, vasomotor dysfunction, and edema and/or sudomotor changes. The second stage occurs approximately 3 to 6 months after the first stage and includes dystrophic changes with continuation of the signs and symptoms associated with stage 1. The last stage is described as atrophic with reduced pain and sensory dysfunction, continued vasomotor dysfunction, and in-

---

creased motor and/or trophic changes. A cluster analysis study showed that CRPS signs and symptoms do not exist sequentially, and that 3 specific CRPS subgroups may exist:

- A predominance of vasomotor dysfunction and motor/tropic changes
- A predominance of sensory abnormalities and neuropathic pain signs and symptoms
- Higher frequencies of signs and symptoms from subgroup 1 and most signs and symptoms of subgroup 2

Further research is warranted to identify separate physiologic mechanisms, diagnostic tools, and therapies specific to each CRPS subgroup.

Pathophysiologic Mechanisms

The pathophysiologic mechanisms for CRPS are complex and remain elusive. One single causative mechanism is unlikely. Many different mechanisms have been proposed for the major signs and symptoms associated with CRPS. Proinflammatory neuropeptides and cytokines such as tumor necrosis factor α and interleukins 1β, -2, and -6 are implicated in the genesis of this syndrome. Peripheral and central sensitization both contribute to the exaggerated pain response and behavioral changes seen in patients with CRPS.

The proposed pathophysiologic mechanisms for CRPS have been described in terms of their impact on the central and peripheral nervous systems. Table 1 describes the proposed pathophysiologic mechanisms of CRPS in the central nervous system, and Table 2 illustrates the proposed pathophysiologic mechanisms of CRPS in the peripheral nervous system.

### Sympathetic Dysfunction

The sympathetic nervous system has a multifactorial role in CRPS. Researchers have associated the hyperalgesia and vasomotor changes with sympathetic dysfunction. Animal models provide direct evidence that adrenoreceptors can be expressed on afferent nociceptors in response to persistent pain. Studies have shown cutaneous injections of norepinephrine induce pain via adrenoreceptors in patients who respond favorably to sympathetic blocks, whereas patients who do not respond to sympathetic blocks are unresponsive to norepinephrine. These data imply that CRPS involves pathologic adrenoreceptors expressed on nociceptors that when stimulated by circulating catecholamines, eg, norepinephrine, cause hyperalgesia and, perhaps, allodynia.

Additional research demonstrated associations between specific vasomotor dysfunctions in patients with acute versus chronic CRPS 1. In the early stages of CRPS 1, increased cutaneous temperature and perfusion values were observed in the affected extremity that were believed to be due to loss of sympathetic vasoconstrictor activity. In chronic CRPS cases, decreased cutaneous temperature and perfusion values in the affected extremity were believed to be due to loss of sympathetic vasoconstrictor activity.

### Table 1. Proposed Pathophysiologic Mechanisms of Complex Regional Pain Syndrome in the Central Nervous System

<table>
<thead>
<tr>
<th>Proposed role</th>
<th>Abnormal characteristics of primary afferents after lesion in CRPS 2, eg, spontaneous discharge, sensitization, ectopic mechanosensitivity, or acquired responsiveness to norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proposed role in spontaneous discharge of sodium channel accumulation in the terminal membrane</td>
</tr>
<tr>
<td></td>
<td>Proposed role of acquired norepinephrine responsiveness in intact C nociceptor terminals whose axons travel in a damaged nerve</td>
</tr>
<tr>
<td></td>
<td>Potential role of an inflammatory reaction and neurogenic inflammation in the acute phase of CRPS</td>
</tr>
</tbody>
</table>

### Table 2. Proposed Pathophysiologic Mechanisms of CRPS in the Peripheral Nervous System

<table>
<thead>
<tr>
<th>Proposed role of N-methyl-D-aspartate receptor–mediated hyperexcitability in the spinal cord dorsal horn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord neuron hyperexcitability can account for pain that has a distally generalized distribution.</td>
</tr>
<tr>
<td>A persistent source of nociceptor drive may maintain hyperexcitability in central neurons.</td>
</tr>
<tr>
<td>Unilateral inhibition of central sympathetic vasoconstrictor activity is involved in vascular abnormalities.</td>
</tr>
<tr>
<td>Motor abnormalities are generated in the central nervous system.</td>
</tr>
</tbody>
</table>

It has been speculated that psychophysical mechanisms are related to sympathetic dysfunction, behavioral disturbances, and persistent pain in patients with CRPS. In addition to the up-regulation of vasoconstrictor adrenoreceptors producing cool and pale skin, sympathetic receptor expression on afferent nociceptive fibers causes spontaneous pain. This pain results in increased circulating catecholamines that potentially may exacerbate the sympathetically mediated symptoms. Furthermore, avoidance behaviors because of the pain may result in a decreased range of motion in the affected extremity.
Treatment Approaches
Certified Registered Nurse Anesthetists (CRNAs) have a role in preventing CRPS and providing symptom management. When individualizing the anesthetic care plan, CRNAs must recognize patients with a history of CRPS and patients who are at risk for the development of CRPS. Precautions such as avoidance of vascular access procedures and blood pressure measurement on affected extremities should be taken. Analgesic requirements for patients with CRPS, as for other patients with chronic pain, may be significantly increased. Preliminary evidence shows a predictive value between the intensity of preoperative knee pain and the development of CRPS after total knee arthroplasty. Another documented risk factor for CRPS is a family history of CRPS in patients younger than 50 years. Several case reports have been published that identify potential risk factors such as antecedent infections that raise the level of autoantibodies; chronic inflammatory disorders, such as rheumatoid diseases; bone metabolic disorders; and amyotrophic lateral sclerosis. One study found an association between antecedent reports of headaches and the development of CRPS.

If a person has a history of CRPS or has known risk factors, measures to reduce reoccurrence or exacerbation should be instituted. It is recommended to delay surgery on an affected extremity until the signs and symptoms of CRPS are reduced at rest and perfusion is optimized. Interventions such as physiotherapy, peripheral vasodilators, sympathetic blockade, and analgesia can help to achieve optimized mobility, perfusion, and pain relief before surgery. These interventions have been associated with reduced postoperative incidence of CRPS.

Regional anesthesia may be more appropriate because of the blockade of sympathetic outflow seen with regional blocks. However, not all regional techniques are completely sympatholytic. For example, carpal tunnel surgery performed under local anesthesia does not result in complete sympathetic blockade and has been associated with high reoccurrence rates of CRPS. In such cases, a stellate ganglion block has reduced reoccurrence rates. A prospective, double-blind, randomized study found that intravenous regional blocks using lidocaine with clonidine were more effective than blocks with lidocaine alone in reducing the reoccurrence rate of CRPS after hand surgery. Similar findings have been reported related to the use of epidural blocks and decreased reoccurrence of CRPS after lower extremity surgery. In addition, pharmacologic therapies may be implemented preemptively and/or postoperatively in patients with CRPS. Several pharmacologic therapies have been used to reduce the incidence of CRPS after high-risk surgery, eg, vitamin C, calcitonin, dimethyl sulfoxide, N-acetylcysteine, mannitol, and carnitine.

Vitamin C was effective in a prospective, randomized, double-blind placebo-controlled study of 217 patients with wrist fractures. The patients received vitamin C or a placebo, and statistically significant incidences of 7% and 22%, respectively, for the development of CRPS were found. Several interventional and pharmacologic therapies exist for patients with CRPS. These therapies are described in Table 3.

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine may have a role in alleviating severe pain among inpatients with CRPS who are unresponsive to traditional therapies. A retrospective study examined 33 patients with CRPS treated with subanesthetic ketamine infusions and found that 76% of patients experienced complete relief of their pain, while 18% had partial relief and 6% had no relief. Furthermore, 100% of the patients who underwent repeated courses of therapy had complete relief of CRPS pain. The duration of effect was longer than 3 months in 54% of patients, and with repeated courses, 33% of patients were pain-free for longer than 3 years. As previously described, spinal cord NMDA receptors are implicated in central sensitization modifications in response to sustained noxious nociceptor stimulation. The authors concluded that prolonged ketamine infusions may block the exaggerated effects of glutamate on the NMDA receptor and potentially reverse the central changes associated with windup mechanisms.
Conclusion

The etiologic factors for CRPS may include inflammatory responses, peripheral and central sensitization, and sympathetic dysfunction. Proinflammatory neuropeptides and cytokines such as tumor necrosis factor α and interleukins 1β, -2, and -6 are also implicated in the genesis of this syndrome. Peripheral and central sensitization both contribute to the exaggerated pain response and behavioral changes seen in patients with CRPS. Central expression of neuropeptides and cytokines induces sensitization and neuronal plasticity, with structural changes resulting in dorsal horn neurons. Other brain abnormalities in patients with CRPS may include atrophic changes in the insula, ventromedial prefrontal cortex, and nucleus accumbens. The sympathetic nervous system has a multifactorial role in CRPS, including hyperalgesia and vasomotor changes associated with this syndrome.

Surgery involving limbs affected by CRPS should be delayed until the signs and symptoms of CRPS are reduced at rest and perfusion is optimized. Interventions such as physiotherapy, peripheral vasodilation, sympathetic blockade, and analgesics can help achieve optimized mobility, perfusion, and pain relief before surgery. Pharmacologic therapies that have been used to reduce the incidence of CRPS after surgery include vitamin C, calcitonin, dimethyl sulfoxide, N-acetylcysteine, manitol, and carbamazepine.

Interventional and pharmacologic therapies for patients with CRPS include nerve blocks, spinal cord and peripheral nerve stimulation, pump implantation, chemical and surgical sympathectomy, and deep brain stimulation. Peripheral nerve blocks and other sympatholytic therapies are believed to be efficacious for the treatment of sympathetically mediated pain in CRPS 1. Other pharmacologic therapies may include bisphosphonate compounds, adrenergic drugs such as phenolamine, systemic steroids, various antidepressants, antiseizure drugs, and various narcotics and benzodiazepines.

This complex syndrome continues to challenge people afflicted with it and their treating clinicians. As the pathophysiologic mechanisms of CRPS are further elucidated, additional treatment modalities may emerge that provide long-lasting relief for patients with CRPS.

REFERENCES

27. Huysgen FJ, De Bruijn AG, De Bruin MT, Groeneweg JG, Klein J,


AUTHORS

Daniel E. Watts, RN, BS, is a student in the Rush University College of Nursing Nurse Anesthesia Program in Chicago, Illinois. Email: Daniel_Watts@rush.edu.

Michael J. Kremer, CRNA, PhD, FAAN, is professor and director of the Nurse Anesthesia Program in the Rush University College of Nursing, and is a staff nurse anesthetist at Rush University Medical Center in Chicago, Illinois. Email: Mike_J_Kremer@rush.edu.